IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Group Art Unit 1634

In re

Patent Application of

Rex M. Bitner, et al.

Application No. 09/475,958

Confirmation No.: 7117

Filed: December 30, 1999

Examiner: Bradley L. Sisson

"CELL CONCENTRATION AND LYSATE CLEARANCE USING PARAMAGNETIC PARTICLES"

I, LESLIE RECTOR hereby certify that this correspondence is being deposited with the US Postal Service as first class mail in an envelope addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date of my signature.

Leslie Rector
Signature

February 11, 2005
Date of Signature

DECLARATION OF REX M. BITNER, UNDER 37 CFR § 1.132

Mail Stop Amendments
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Rex M. Bitner, do hereby declare and state the following:

1. Since 1997, I have worked at Promega Corporation, Madison, WI, as a Senior Scientist and as Technology Manager of Research and Development, the assignee of the above-identified patent application.

2. I received my Ph.D. in Genetics from the University of California-Davis in 1978. I have worked extensively with, and conducted research on, methods for purifying cellular components. I consider myself an expert in the biochemistry and molecular biology of cells, and method of purifying cellular components. Attached hereto as Exhibit A, and incorporated herein by reference, is a copy of my Curriculum Vitae.

3. I am a joint inventor of the subject matter of all the claims pending in the above-identified patent application, i.e. claims 1-25, and 27-29. I am also a joint inventor of the

subject matter of all the pending claims after amendment, as proposed in the accompanying response to non-final Office Action, to be submitted herewith.

4. I have reviewed the Office Action, stamped with a mailing date of August 11, 2004 (hereinafter, "Office Action"). For reasons stated below, I am of the opinion that one of reasonable skill in the art would have no difficulty in identifying the material intended to be incorporated by reference in the documents that were incorporated by reference in the above-mentioned application, such documents including US 6,310,199 (hereinafter the '199 patent), and PCT/US98/01149 (WO 98/31840) (hereinafter PCT 01149).

5. The '199 patent document was incorporated by reference in the above-mentioned application as follows:

> "Such preferred ion exchange ligands and pH dependent ion exchange matrices which incorporate such ligands are described in U.S. Patent Application Ser. No. 09/312,172, now U.S. Patent No. 6,310,199, for an invention titled pH DEPENDENT ION EXCHANGE MATRIX AND METHOD OF USE IN THE ISOLATION OF NUCLEIC ACIDS, incorporated by reference herein, an application filed concurrently with the provisional patent application on which the present non-provisional patent application is based."

While the entire '199 Patent was incorporated by reference, we refer specifically to "ion exchange ligands and pH dependent ion exchange matrices which incorporate such ligands" as guidance for locating the relevant information. It is my belief, as one of reasonable skill in the art, that one skilled in the art could identify that material within the '199 Patent that relates to pH dependent ion exchange particles. Specifically, one skilled in the art would appreciate that we were intending to refer to Examples 3, 5, or 7 of the '199 Patent. Example 3 of the '199 patent is entitled "Synthesis Of Porous Silica Magnetic pH Dependent Ion Exchange Particles" and the preparation of glycidyl modified silica magnetic particles, glycidyl-histidine modified silica magnetic particles, glycidyl -alanine modified silica magnetic particles and glycidyl -cysteine modified silica magnetic particles is therein described. Example 5 is entitled "Preparation of Porous Silica Magnetic Urea-Linked pH Dependent Ion Exchange Particles" and describes the preparation of silica magnetic particles linked to histidine through urea, histamine and propionate, and histidine and propionate.

Example 7 is entitled "Isolation of Plasmid DNA Using Porous Silica Magnetic Glycidyl-Histidine pH Dependent Ion Exchange Particles" and describes the use of silica magnetic particles in isolating plasmid DNA.

The entire '199 Patent was incorporated by reference simply to reduce the volume of the above-mentioned application. For instance, example 3 of the present application provides detailed descriptions of and detailed procedures for the manufacture of glycidyl-histidine and glycidyl-alanine modified silica magnetic particles. Accordingly, it is my belief that incorporation of the patent was not necessary to describe the claimed invention or to provide an enabling disclosure.

6. The PCT 01149 document was incorporated by reference in the above-mentioned application as follows:

> "For methods of adsorption and desorption of target nucleic acids to silica magnetic particles, which are suitable for use in the present invention, see international patent application number PCT/US98/01149 for METHODS OF ISOLATING BIOLOGICAL TARGET MATERIALS USING SILICA MAGNETIC PARTICLES, published as WO 98/31840, incorporated by reference herein."

While the entire PCT 01149 document was incorporated by reference, we refer specifically to "methods of adsorption and desorption of target nucleic acids to silica magnetic particles" as guidance in the above-mentioned application. The invention described in the instant application describes methods for cell concentration as well as lysate clearance, and after these procedures, the adsorbtion and desorbtion of target nucleic acids may take place, as exemplified by PCT 01149. In my opinion as one of reasonable skill in the art, one of ordinary skill in the art would have no difficulty in identifying which parts of PCT 01149, were intended to be incorporated by reference. In particular, one of ordinary skill in the art would appreciate that examples 4, 5 and 6 of PCT 01149 provide specific examples of how the concentrated cells or cleared lysate provided by the instant invention can be further processed to purify target nucleic acids, such as plasmid DNA (examples 4 and 5) and RNA (example 6). Additionally, because examples 4 and 5 use centrifugation (which is both time consuming and labor intensive) to concentrate cells and clear cell lysates of debris, one of ordinary skill in the art would understand that PCT 01149 also provides specific examples of how the instant invention provides advances over the prior art.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: February 3, 2005 Rex M Bitner

Rex M. Bitner

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EXHIBIT A

REX M. BITNER, Ph.D.
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QUALIFICATIONS SUMMARY

Over twenty years of industrial experience in biotechnology research and product development at Promega (Madison, WI), Amersham Pharmacia Biotech, (Milwaukee, WI), and 3M (St. Paul, MN). Four years of postdoctoral research in molecular biology at the University of Colorado, Boulder and the University of California, Davis. Broad, in-depth knowledge of molecular biology, solid phase extraction of biological materials, and all phases of product development in an ISO2000 environment. Experienced in supervising a biosafety level 3 laboratory, development and evaluation of intellectual property, project management, and the development, launch and care for biotechnology products. Additional experience in the management of intellectual property, including patent application office actions, interviews with USPTO examiners, as well as foreign patent opposition hearings, both as patentee and as an opposition party.

PROFESSIONAL HISTORY

1997 - present **PROMEGA CORPORATION, Madison, Wisconsin**

Senior Scientist and Technology Manager (1997 - present)

Technology Manager and Senior Project Manager, Genetic Analysis: development of separation technologies, intellectual property, and purification products for the biotechnology marketplace and clinical laboratory market, with particular emphasis on automation of nucleic acid purification products for use in genomics, high throughput pharmaceutical drug screening, and clinical diagnostics applications. Development of pH dependent ion exchange purification systems using both column and paramagnetic particle purification methods in robotic workstations, with additional emphasis on automated cell concentration and magnetic clearing of cellular lysates in 96-well walkaway automated DNA purification (particularly using Beckman BioMek® FX and Tecan Genesis® robotic platforms). Products developed for genomic DNA purification from human whole blood and tissues (including R&D Magazine's R&D 100 award winning DNA-IQ™(for 2002), plant materials, and DNA purification from food ingredients for use in the quantitative detection of genetically modified organisms (GMO) in food. Additional experience with DNA sequencing automation, RNA purification, and PCR cleanup, particularly using Beckman, Tecan and Thermo-Electron Labsystems robotic platforms.

Project leader for recent Promega products, in an ISO9001 or ISO2000 environment, including:

Wizard® Genomic, 10ml blood	A1620	Wizard® Magnetic DNA Purification for Food	FF3751
Wizard® Magnetic 96 DNA Plant	FF3761	MagneSil® Blood Genomic, Max Yield	MD1360
MagneSil® ONE, Fixed Yield	MD1370	MagneSil® KF, Genomic System	MD1460
Deep Well MagnaBot® 96 Magnet	V3031	PureYield™ Plasmid Midi-Prep System	A2495

Developed a variety of inventions which are used in Promega's nucleic acid purification products (please see details in patent section below). Intellectual property management as Technology Manger has included USPTO and foreign patent office actions, in person interviews with USPTO patent examiners, as well as participation in foreign patent opposition proceedings, both as the patentee and as an opposition party, including as an opposition member in the appeal of an invalidated patent. The efficient integration of foreign patent filing strategies and licensing of intellectual property within Promega's Genetic Analysis business strategy has been a central responsibility.

PROFESSIONAL HISTORY, continued

1995 - 1997 **AMERSHAM PHARMACIA BIOTECH INC., Milwaukee, Wisconsin.**

Senior Research Scientist (1995 - 1997)

Senior Research Scientist and Project Leader responsible for nucleic acid purification products for the biotechnology laboratory: development of novel separations matrices and processes, formulation and execution of project plans, maintenance of timelines and scheduling, and supervision of personnel on several project teams. Research and development of new products for the molecular biology marketplace, particularly in the areas of proprietary purification products, anion exchange chromatography, and solid phase extraction and immobilization of nucleic acids. Responsibilities included the management of personnel, timelines and ISO 9001 documentation of product development.

1982 - 1994 **3M COMPANY, St. Paul, Minnesota.**

Research Specialist (1984 - 1994)

Identifying, planning and pursuing molecular biology programs of interest to 3M businesses. Research programs involved diverse product objectives: Development of 3M's Rapid Attest™ biological/sterilization monitor product, GMP purification of bovine phosphophoryn proteins (for bone repair), genetic manipulation of bacteria to produce specialty chemicals (*meta*-hydroxyphenylacetylene, and aromatic compounds useful in laser dyes), cDNA cloning of mammalian genes for drug discovery screening, surface immobilization of nucleic acids onto ceramic oxide/3M Empore™ (PTFE) membranes (for use in DNA blotting, hybridization and sequencing), solid phase extraction of DNA for automated sequencing, solid phase extraction of DNA from human blood plasma for use in PCR, protein immobilization on azlactone functionalized porous beads (including 3M Emphaze™ beads and network beads), and cloning of stress protein genes from bacteria associated with periodontal disease. Development and implementation of DNA purification technologies in conjunction with 3M's partnership with Diagen / Qiagen. Over ten years experience supervising a biosafety level 3 containment laboratory.

Other responsibilities included evaluation of both internal and external research proposals and intellectual property. Additional responsibilities as Institutional Biosafety Officer, OSHA blood-borne pathogen safety officer, and as scientific advisor in the development of and compliance with Minnesota State (Environmental Quality Board) regulations governing recombinant organisms.

Senior Biologist (1982 -1984)

Responsibilities included setting up and staffing a recombinant DNA laboratory, evaluation of outside business proposals and intellectual property issues, and initiation of new research programs in molecular biology: gene expression in *Bacillus subtilis*, and R&D of 3M's Rapid Attest™. Additional responsibilities: initiation of university research contracts and management of laboratory personnel.

1978 - 1982 **UNIVERSITY OF COLORADO, Boulder, Colorado.**

Postdoctoral research: Dr. Peter L. Kuempel, Dept. of Molecular, Cellular, and Developmental Biology: Termination of chromosome replication in *E. coli*.

PROFESSIONAL HISTORY, continued

1974 - 1978 **UNIVERSITY OF CALIFORNIA, Davis, California.**

Postdoctoral research: Dr. Gordon G. Edlin, Dept. of Genetics (1978).
Instructor: Department of Genetics (1977).

1974 **UNIVERSITY OF WASHINGTON, Seattle, Washington**
Post-graduate Research Assistant: Dr. Jonathan A. Gallant, Dept. of Genetics

EDUCATION

Ph.D. in Genetics, Phi Kappa Phi, 1978
University of California, Davis, California

B.S. in Biology, *cum laude*, 1974
University of Washington, Seattle, Washington

PATENTS

Rex M. Bitner, Daniel Simpson, Roderick Flemming and Susan Koller. US 6,787,307, CA 2428532, AU 2594202 and International Publication Number 00238758WO. Lysate Clearance and Nucleic Acid Isolation using Silanized Silica Matrices.

Rex M. Bitner, Jacqui Sankbeil, Braeden Butler, Doug White, Craig Smith. US 6,284,470, EP1179058, EP1341910 and International Publ. Number 00070040 WO. Cell Concentration and Lysate Clearance Using Paramagnetic Particles.

Tereba, Allan, Rex M. Bitner, Susan C. Koller, Craig E. Smith, Daniel D. Kephart, Steven J. Ekenberg. US 6,673,631 B1, CA 2379503, EP 1204741, and PTC Applic. Number 00114590 WO. Simultaneous Isolation and Quantitation of DNA.

Smith, Craig E., Diana Holmes, Dan Simpson, Jehoshua Katzenhendler, Rex M. Bitner, Josephine Grosch. US 6,806,362, US 6,310,199, EP1179057, AU5126100 and International Publication Number 00069872 WO. pH Dependent Ion Exchange Matrix and Its Use in the Isolation of Nucleic Acids.

Smith, Craig E., Diana Holmes, Dan Simpson, Jehoshua Katzenhendler, Rex M. Bitner, Josephine Grosch. US 6,376,194, US 6,270,970, EP1179056, AU4841500 and International Publication Number 00070041 WO. Mixed Bed Solid Phase and Its Use in the Isolation of Nucleic Acids.

Smith, Craig E., Donald A. Creswell, Rex M. Bitner, Douglas H. White, Braeden L. Butler, Scott A. Lesley. US 6,194,562, EP1071695, CA 2329067, and International Patent Number 99918650 WO. Endotoxin Reduction in Nucleic Acid Purification.

Bitner, Rex M., Chan-Wha Kim, and Michael G. Williams. EP647232B1, CA 2,136,432 and International Patent Application PCT/US93/04576. Applicant: Minnesota Mining and Manufacturing, St. Paul, MN. Deproteinization with azlactone-functional supports.

PATENTS, continued

Bitner, Rex M. and Eric F. Funkenbusch. European Patent Application Number 90303382.7. Applicant: Minnesota Mining and Manufacturing Company, St. Paul, MN. Metal oxide supports for nucleic acids.

PUBLICATIONS

Bitner, R. M. and S.C. Koller. 2004. "Automated high throughput purification of genomic DNA from plant leaf or seed using Promega's MagneSil® paramagnetic particles", Proceedings of SPIE, Microarrays and Combinatorial Techniques: Design, Fabrication and Analysis II, Vol 5328, p. 78-86.

Bitner, R., S. Koller, J. Sankbeil, M. Denhart and H. Shenoi. 2004. "Purifying Genomic DNA from Whole Blood on Automated, High-throughput and Moderate-throughput Platforms". Journal of Laboratory Automation, Vol 9, p. 64-71.

Smith, C., P. Otto, R. Bitner and G. Shiels. 2003. "Chapter 9: DNA Purification", in PCR Primer: A Laboratory Manual 2nd Edition, editors: Carl W. Dieffenbach and Gabriela S. Dveksler, Cold Spring Harbor Laboratory Press, ISBN 0-87969-6532, p.87-115.

Bitner, R., S. Koller, and J. Sankbeil. 2003. "Automated high throughput purification of genomic DNA from whole blood using Promega's MagneSil® paramagnetic particles with either the Max Yield of MagneSil® ONE normalized purification methods"in Microarrays and Combinatorial Technologies for Biomedical Applications: Design, Fabrications and Analysis, Proceedings SPIE 4966, p. 98-105.

Bitner, R.M. and S.C. Koller. 2002. "Automated genomic DNA purification options in agricultural applications using MagneSil™ paramagnetic particles. Tools for Molecular Analysis and High-Throughput Screening Proceedings of SPIE Vol. 4626 p. 218-225.

Bitner, R. and S. Koller. 2001. "Automation of DNA Extraction from Food and Plants Using MagneSil™ Paramagnetic Particles" Genomics and Proteomics Technologies, *Proceedings of SPIE* Vol 4264 p. 9-16.

Bitner, R., D. White, S. Krueger, M. Bjerke, B. Butler, C. Smith. 2000. " Use of MagneSil™ Paramagnetic Particles for Plasmid Purification, PCR Cleanup and Purification of Dideoxy and Big Dye DNA Sequencing Reactions" Advances in Nucleic Acid and Protein Analyses, Manipulation and Sequencing, *Proceedings of SPIE* Vol 3926 p. 126-133.

Williams, M.G., P.E. Olson, K.J. Tautvydas, R.M. Bitner, R.A. Mader, and L.P. Wackett. 1990. "The application of toluene dioxygenase in the synthesis of acetylene terminated resins" Appl Microbiol Biotechnology *34*: 316-321.

Bitner, R.M. and P.L. Kuempel. 1982. "P1 Transduction Mapping of the *trg* Locus in *rac*$^+$ and *rac*$^-$ Strains of *Escherichia coli* K-12" J. Bacteriol. *149*: 529-533.

Bitner, R.M. and P.L. Kuempel. 1981. "P1 Transduction Map Spanning the Replication Terminus of *Escherichia coli* K-12" Mol. gen. genet. *184*: 208-212.

Binding, R., G. Romansky, R. Bitner and P. Kuempel. 1981. "Isolation and Properties of Tn*10* Insertions in the *rac* Locus of *Escherichia coli*" Mol. gen. genet. *183*: 333-340.

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Edlin, G., L. Lin and R. Bitner. 1977. "Reproductive Fitness of P1, P2 and Mu Lysogens of *Escherichia coli*" J. Virol. *21*: 560-564.

Lin, L., R. Bitner and G. Edlin. 1977. "Increased Reproductive Fitness of *Escherichia coli* Lambda Lysogens" J. Virol. *21*: 554-559.

Gallant, J.A., L. Shell and R. Bitner. 1976. "A Novel Nucleotide Implicated in the Response of *E. coli* to Energy Source Downshift" Cell *7*: 75-84.